REMARKS

Upon entry of the foregoing amendments, claims 2-5 and 7-21 are pending in the present application. In this response, claims 1 and 6 have been cancelled, and claims 2, 3, 5, 7, 8, 10, 14, 15 and 21 have been amended. The amended claims are fully supported throughout the instant specification. Accordingly, no new matter has been added.

DRAWINGS

Applicants acknowledge the Draftsperson's objection to the Drawings filed in the present application. In compliance with 37 CFR 1.84 and 1.85, Applicants have submitted corrected drawings to the Official Draftsperson and have provided a copy of the corrected drawings with the instant response. Therefore, Applicants request reconsideration and withdrawal of this objection.

RESPONSE TO ARGUMENTS

Applicants note with appreciation that the Examiner has withdrawn the rejection of claims 1-21 under 35 U.S.C. §112, first paragraph and 35 U.S.C. §103.

THE 35 U.S.C. §112, SECOND PARAGRAPH REJECTIONS

The Examiner has rejected claims 1-21 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner specifically states that the claims are unclear for reciting the terms "signal site" and "signal sequence", interchangeably and for a lack of antecedent basis for these terms (*see*, Office Action at page 4). Applicants traverse.

However, to facilitate prosecution of this application, Applicants have amended pending claim 2 and 5 to recite only "signal sequence" as suggested by the Examiner (*see*, Office Action at page 5). Applicants thank the Examiner for this suggestion and respectfully request withdrawal of the present rejection.

THE 35 U.S.C. §102 REJECTIONS

The Examiner has rejected claims 1, 2, 5-13 and 18-20 under 35 U.S.C. §102(b) as being anticipated by US Patent No. 5,629,159 ("Anderson") as evidenced by Kilby *et al.*, *Trends Genet.* 9: 413-421, 1993 ("Kilby"). Specifically, the Examiner states that Anderson teaches a nucleic acid molecule comprising a first recombinase signal sequence and a second recombinase signal sequence, and a recombinase gene operably linked to an expression control sequence. The Examiner also states that Kilby demonstrates the loss of recombinase activity upon excision (*see*, Office Action at page 6-7). Applicants traverse.

Applicants have herewith cancelled claims 1 and 6 and have amended claim 2 to recite a nucleic acid molecule comprising a first and a second signal sequence that are positioned to mediate excision or inversion of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase, which decreases or eliminates recombinase-mediated toxicity. Anderson teaches the excision of an immortalization gene using a first and second recombinase signal sequence where the sequence can be LoxP or FRT. However, Anderson does not specifically teach the excision or inversion of either a recombinase gene or an expression control sequence. While the Examiner points to the constructs of Figure 3C and 6A to support his position, Applicants assert that Anderson teaches the use of these constructs to specifically excise an immortalization gene. Anderson does not teach or suggest the excision or inversion of a recombinase gene or an expression control sequence. Furthermore, Anderson does not teach or suggest the use of signal sequence mediated excision or inversion of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase in order to decrease or eliminate recombinase-mediated toxicity. In contrast, the present specification teaches that cell toxicity; cell proliferation; and genomic or chromosomal instability are decreased or eliminated following recombinase-mediated excision or inversion of either a recombinase gene or expression control sequence (*see, e.g.*, pg. 4, lines 11-18; pg. 5, lines 3-12; Table 1, pg. 10; Example 1, pg. 32, line 22 - pg. 34, line 19; Example 2, pg. 34, line 23 - pg. 35, line 1; Example 3, pg. 39 line 20 -pg. 40, line 21). Moreover, Anderson does not teach or suggest the inversion of a recombinase gene or expression control sequence, whereas, the present specification teaches that the inversion of a recombinase gene or expression control sequence would decrease or eliminate expression of the encoded recombinase. The instant specification also

teaches the addition of additional recombinase would re-invert the coding sequence and re-establish expression (*See*, Specification pg. 7, lines 1-10; pg. 16, lines 4-17).

Applicants also contend that, while Kilby teaches that an excised nucleic acid would be quickly lost *in vivo*, Kilby alone or in combination with the teachings of Anderson, does not teach or suggest the decrease or elimination of recombinase-mediated toxicity following inversion or the decrease of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase.

Thus, Anderson and/or Kilby do not teach or suggest all of the limitations of the claimed invention. Accordingly, Applicants assert that claim 2, as amended herein (and claims 5, 7-13 and 18-20, which depend from claim 2) are not anticipated by Anderson as evidenced by Kilby. Therefore, this rejection of these claims should be withdrawn.

The Examiner has also rejected claims 1-8 under 35 U.S.C. §102(b) as being anticipated by either one of WO 97/06271 ("Choulika") as evidenced by US Patent 6,200,800 ("Choulika '800") or Russ *et al.*, *J. Virol.* 70(8): 4927-4932 ("Russ") as evidenced by Kilby. Specifically, the Examiner asserts that Choulika and Russ teach a nucleic acid molecule comprising a first and second recombinase signal sequence flanking the recombinase encoding sequence and the expression control sequence such that expression of the recombinase results in excision and extinguishing recombinase activity. According to the Examiner, Choulika '800 teaches that, the recombinase system can used can be CreLox or FLP, and Kilby teaches the loss of recombinase activity upon excision (*See*, Office Action at page 8-9). Applicants traverse.

As discussed above, Applicants have cancelled claims 1 and 6 and have amended claim 2 to recite a nucleic acid molecule comprising a first and second signal sequence that are positioned to mediate excision or inversion of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase, which decreases or eliminates recombinase-mediated toxicity. Choulika and Russ teach a loxP site in the 3'LTR sequence U3 with the gene to be inserted into a cell. As described, Choulika and Russ do not specifically teach the excision or inversion of either a recombinase gene or of an expression control sequence. The Examiner cited the teachings of Choulika and Russ, wherein a loxP site is included in the 3'LTR U3 region, which permits the packaging of a retrovirus without excision of the recombinase gene.

However, neither reference teaches or suggests, the use of signal sequence mediated excision or inversion of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase in order to decrease or eliminate recombinase-mediated toxicity. In contrast, the present specification teaches that cell toxicity; cell proliferation; and genomic or chromosomal instability are decreased or eliminated following recombinase-mediated excision or inversion of either a recombinase gene or an expression control sequence.

Applicants also contend that, while Kilby teaches that an excised nucleic acid would be quickly lost *in vivo* and Choulika '800 teaches that a recombinase system can include CreLox sites or FLP sites, neither reference, alone or in combination with the teachings of Russ and Choulika, respectively, teaches or suggests that the decrease or elimination of recombinase-mediated toxicity following inversion or decrease of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase.

Accordingly, Applicants assert that claim 2, as amended herein (and claims 3-5, 7 and 8, which depend from claim 2) are not anticipated by Choulika as evidenced by Choulika '800 or Russ as evidenced by Kilby and request reconsideration and withdrawal of the present rejection. Therefore, the rejection of these claims should be withdrawn.

The Examiner has also rejected claims 1, 2, 5-13 and 18-20 under 35 U.S.C. §102(a) as being anticipated by Bunting *et al.*, *Genes & Development* 13(12): 1524-1528, 1999 ("Bunting") as evidenced by Kilby. Specifically, the Examiner states that Bunting teaches a nucleic acid molecule comprising a first and second recombinase signal sequence flanking a recombinase encoding sequence as well as the transformation of ES cells with such a described nucleic acid molecule. The Examiner further states that Bunting teaches that a neomycin resistance gene can be positioned between the recombinase signal sequences such that expression of the recombinase excises the neomycin resistance gene. Moreover, according to the Examiner, Kilby teaches the loss of recombinase activity upon excision (*see*, Office Action at page 9-10). Thus, the Examiner concludes that the ES cells of Bunting anticipated the claimed cells. Applicants traverse.

Applicants have cancelled claims 1 and 6 and have amended claim 2 to recite a nucleic acid molecule comprising a first and second signal sequence that are positioned to mediate excision or inversion of either a recombinase gene or the expression control sequence when the

signal sequences are contacted with a recombinase, which decreases or eliminates recombinase-mediated toxicity, as discussed above. As described, Bunting does not specifically teach the excision or inversion of either a recombinase gene or an expression control sequence. The Examiner has indicated that Bunting teaches signal sequences flanking a recombinase encoding sequence and a target sequence, which can be a neomycin resistance gene, such that expression of the recombinase excises the neomycin resistance gene. However, Bunting does not teach or suggest, the ability of signal sequence mediated excision or inversion of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase to decrease or eliminate recombinase-mediated toxicity. As noted, the present specification teaches that cell toxicity; cell proliferation; and genomic or chromosomal instability are decreased or eliminated following recombinase-mediated excision or inversion of either a recombinase gene or expression control sequence.

Applicants also contend that, while Kilby teaches that an excised nucleic acid would be quickly lost *in vivo*, Kilby, alone or in combination with the teachings of Bunting does not teach or suggest the decrease or elimination of recombinase-mediated toxicity following inversion or decrease of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase.

Thus, Bunting and/or Kilby do not teach all of the limitations of the claimed invention. Accordingly, Applicants assert that claim 2, as amended herein (and claims 5, 7-13 and 18-20, which depend from claim 2) are not anticipated by Bunting as evidenced by Kilby. Therefore, this rejection of these claims should be withdrawn.

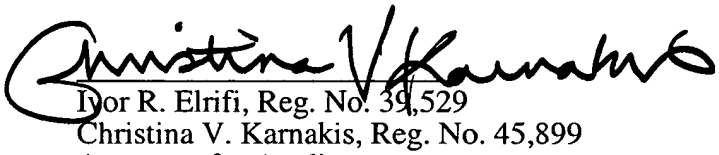
ALLOWABLE SUBJECT MATTER

As suggested by the Examiner to overcome the rejections under 35 U.S.C.§112, second paragraph, and to include all of the limitations of the base claim and intervening claims, Applicants have amended claims 14-17 and 21. Applicants thank the Examiner for this suggestion and respectfully submit that these claims are now in condition for allowance.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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